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Factors That Influence the Determination of Residual Solvents in Pharmaceuticals by Automated Static Headspace Sampling Coupled to Capillary GC–MS

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Abstract

The impact of several experimental parameters on static headspace sampling for volatile impurities is discussed. Figures of merit are provided for some common organic solvents dissolved in dimethylacetamide. The performance is compound specific, but in the best case, detectability is about 0.2 mg/L with the mass spectrometer operating in the scanning mode. Sensitivity improves by about a factor of 50 when single ion monitoring is used. Linearity extends for about 4 orders of magnitude. This system is used to determine acetone as a residual solvent in the sulfonamide antibiotic, sulfamethazine, at levels of 1 to 15 mg/kg with precision of 3 to 5%.

Introduction

To assist in the process of detecting and preventing the illicit manufacture and distribution of bulk pharmaceuticals, analytical techniques are being developed and applied to characterize these materials in terms of impurities that either enter into or are produced during the manufacturing process. It is anticipated that, in this manner, a "signature" or "fingerprint" of a specific manufacturer and specific production lot can be determined. One area of interest concerns the identification and quantitation of organic volatile impurities, such as residual solvents, that remain in the finished drug.

A number of "official" methods have been established for the determination of select organic volatiles in pharmaceuticals (1–4). The tolerance level for these impurities is 100 mg/kg in the bulk drug, with the following exceptions: benzene, chloroform (50 mg/kg), 1,4-dioxane, methylene chloride, and trichloroethylene. Gas chromatography (GC) is used to analyze either an aliquot of a solution of the drug in a suitable solvent or an aliquot of vapor derived from a solution of the drug. The aliquot of vapor is obtained by either dynamic headspace sampling (i.e., purge and trap) or static headspace sampling. Headspace methods minimize wear and tear on the chromatographic system because only the volatile portion of the sample is subject to analysis. This relaxes constraints on sample preparation and reduces the possibility of artifact formation (5).

Static headspace sampling (6–9) is conducted by sealing the material to be evaluated in a vessel and incubating the system at a fixed temperature until the volatile analyte has equilibrated between the vapor headspace and the liquid (or solid) sample. An aliquot of the vapor is withdrawn for analysis. Commercial instruments that enhance the precision of the method by automating the entire process are available. Dynamic headspace methods purge the system with gas during sampling and collect the evolved materials on a trap prior to analysis. This approach is inherently more sensitive than equilibrium methods and may be most appropriate for the analysis of some solid materials such as polymers (10), but it is not readily automated and is generally restricted to aqueous solutions. There are advantages in terms of heat transfer and mass diffusion to dissolving the test material in a suitable solvent. Although water is generally a good solvent for pharmaceuticals, it is not a universal one.

A number of authors have described the use of static headspace sampling for the determination of residual solvents (11–14), and extensive revision and expansion of the official static headspace method has been recently proposed (15–17).

For forensic purposes, there is a need to identify and monitor residual solvents at levels well below the tolerances described above. This work investigates the performance of an automated static headspace sampler coupled to narrow-bore capillary GC with detection by a benchtop mass spectrometer (MS). The impact of several experimental variables (i.e., temperature, solution volume, and time) that affect the performance of the sampler is discussed, and figures are provided for a number of analytes dissolved in dimethylacetamide. This solvent is particularly suitable for certain drugs. Some comparison is made to the behavior of these analytes when dissolved in water. Finally, this paper presents the evaluation of a sulfonamide antibiotic, sulfamethazine, for the residual solvent, acetone.

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Experimental

Instrumentation

An equilibrium headspace autosampler (Model 7000/7050, Tekmar; Cincinnati, OH) was coupled through a cryofocusing module (Tekmar) to a narrow-bore capillary column within a GC (Model 5890 Series II, Hewlett-Packard; Wilmington, DE) that was equipped with sub-ambient cooling. The column was introduced directly into a benchtop MS (Model 5971A mass selective detector, Hewlett-Packard). Data was collected and reduced using DOS-based (Microsoft) software (Version 1034C, Hewlett-Packard) that was running under Windows (Microsoft) on a microcomputer (Vectra Model 386/25, Hewlett-Packard). The headspace autosampler was controlled by software (Teklink 7000, Version 1.0, Tekmar) that was running in the same computer environment. To minimize the reactivity of the sampling system, the autosampler was replumbed with electroform nickel tubing (Tekmar).

Headspace sampler operating conditions

A liquid sample was confined in a 9-mL glass vial that was sealed with a Teflon-lined butyl rubber septum in a crimp cap. After equilibration at a given temperature, helium was added to the vial to raise the pressure to 5 psi, then the headspace was vented through a 0.25-mL sampling loop under a back pressure that was roughly equal to the head pressure on the column. The flow to the column was directed through a 0.25-mL sampling loop (105°C), transfer line (115°C), and capillary union (180°C) to a cryofocusing trap (–110 to –130°C). Sufficient transfer time was allowed for the internal volume of the transfer line to be swept 2.5 times. The analytes were revolatilized by rapidly increasing the temperature to 200°C to initiate the chromatography.

Chromatographic operating conditions

A narrow-bore cross-linked trifluoropropylmethyl polysiloxane column (Rtx-200, 30 m × 0.25-mm i.d., 1000-nm film) (Restek; Bellefonte, PA) was used. This modestly polar column was selective for lone-pair electrons and has been promoted for industrial solvent analysis. It offered a slightly greater thermal stability (–20 to 310°C) than the DB-624 (J&W Scientific; Folsom, CA), which is advocated for the proposed United States Pharmacopeial (USP) method (11).

The flow rate was adjusted to 0.9 mL/min at 50°C using the retention time of carbon dioxide from a cryofocused injection of air as a marker.

The temperature program involved a 2-min hold at 10°C, then a ramp to 200°C at 10°C/min. During analytical runs, the detector was turned off prior to the elution of dimethylacetamide (15 min), and the temperature ramp was increased during the latter part of the runs to shorten analysis time.

Mass spectrometer operating conditions

At the start of each day, the instrument was tuned for general scanning using a self-directed algorithm supplied by the manufacturer. No special effort was made to optimize the system for low mass sensitivity.

Scanning experiments were conducted using a solvent delay of 2 min and a mass range of 20 to 250 amu at a repetition rate of 2.9 Hz.

For some studies, selected ion monitoring (SIM) was used for a major ion in each analyte spectrum with a dwell time of 50 ms and a repetition rate of 12.3 Hz. Only one ion was monitored at a time in a best-case scenario. The ions were as follows: ethanol (45 amu), methylene chloride (84 amu), chloroform (83 amu), acetone (43 amu), benzene (78 amu), trichloroethylene (132 amu), 2-butanone (43 amu), *n*-octane (43 amu), 1,4-dioxane (88 amu), *n*-nonane (43 amu), and chlorobenzene (112 amu).

Standard preparation

Standard solutions were prepared by weight in dimethylacetamide (99.9%, HPLC grade, Aldrich; Milwaukee, WI) from materials that were obtained from chemical supply houses.

To evaluate the system, the following analytes were used: ethanol, methylene chloride, chloroform, acetone, benzene, trichloroethylene, 2-butanone, *n*-octane, *p*-dioxane, and chlorobenzene.

For the quantitation of acetone in sulfamethazine, working standards were prepared in the range of 0 to 60 mg/L, and an internal standard of 2-pentanone was prepared at a concentration of about 30 mg/L.

Sample preparation

For studies of standards, an appropriate volume of dimethylacetamide or water or both was placed into a headspace vial and then spiked with 0.050 mL of the working standard to be evaluated.

Quantitative analysis of acetone in sulfamethazine proceeded as follows. About 0.2 g of drug was placed in a vial, and 0.5 mL dimethylacetamide was added. This was followed by 0.050 mL 2-pentanone (30 mg/L) to serve as an internal standard. The vial was capped and sealed for analysis. All weights were recorded directly into an Excel (Microsoft) worksheet from an electronic analytical balance (Model AE240, Mettler Instruments; Highstown, NJ) that was equipped with an RS-232 data output option (Option 011, Mettler). This transfer was mediated by software (Balance Talk Jr., Version 2.00, Labtronics; Guelph, Ontario, Canada) that was running under Windows (Microsoft).

Results and Discussion

Chromatographic parameters

A chromatogram of the subset of materials that was used for these studies is shown in Figure 1. Retention times and relative retention indexes (18) obtained for other materials analyzed on the Rtx-200 column (trifluoropropylmethyl polysiloxane) are presented in Table I. Data obtained by others (15) on a DB-624 column (6% cyanopropylphenyl, 94% dimethyl polysiloxane) was also included. Direct comparison was limited by differences in the column dimensions and the temperature programs that were used, but it seemed clear that the Rtx-200 column offered increased selectivity for ketones and esters versus other oxygenates, such as alcohols. This factor has been useful in certain

complicated matrices, such as the application of forensic headspace analysis to the characterization of beverages that have been contaminated with cleaning products. However, there was little advantage with respect to residual solvent analysis because the composition of the aliquot derived from the headspace was usually simple. Because the column was directly interfaced to the MS, the flow rate through the system was restricted to less than 1 mL/min. A 0.25-mm i.d. column with as thick a film as possible (1000 nm) was chosen as a compromise between capacity and favorable flow dynamics.

Selection of a suitable solvent

The drug of immediate concern was a sulfonamide antibiotic, sulfamethazine, which is poorly soluble in water (less than 0.1%, w/v) but highly soluble in dimethylacetamide (greater than 40%, w/v). Dimethylacetamide has been recommended as a dissolution medium for residual solvent analysis in pharmaceuticals (17) because of its solubilizing properties, high boiling point (166°C), and purity. We used dimethylsulfoxide (DMSO) as a solvent in some cases. Although DMSO has similar physical properties (19) to dimethylacetamide it contains significant amounts of the impurities, dimethylsulfide (3.8 min) and dimethyldisulfide (8.7 min), under the sampling and analysis conditions previously described.

Effect of volume, temperature, and equilibration time

Studies were conducted using dimethylacetamide to determine the amount of time required for selected analytes to distribute between the solution and the headspace as a function of temperature and volume. It was difficult to control this experiment because any agitation of the vessel led to drastic increases in the effective surface area of the solution and expedited the mass transfer process. Indeed, this factor is exploited in modern instruments that are often equipped with vial shakers. To mimic our anticipated methodology, an aliquot of a stock solution was added to dimethylacetamide in the headspace vial, and the vial was capped, sealed, and vortex mixed (Genie 2, Fisher Scientific; Pittsburgh, PA) for 1 s. This solution was immediately subjected to headspace analysis. Volumes from 0.5 to 4.0 mL were studied at temperatures from 25 to 65°C. In all cases, equilibrium was achieved in less than 10 min without any additional agitation by the instrument. For 0.5-mL volumes at 25°C, significant decreases in the vapor-phase concentration were not observed until the equilibration interval was below 5 min. In some cases, when samples were equilibrated for50 min, slight apparent decreases were observed, which may be indicative of leakage.

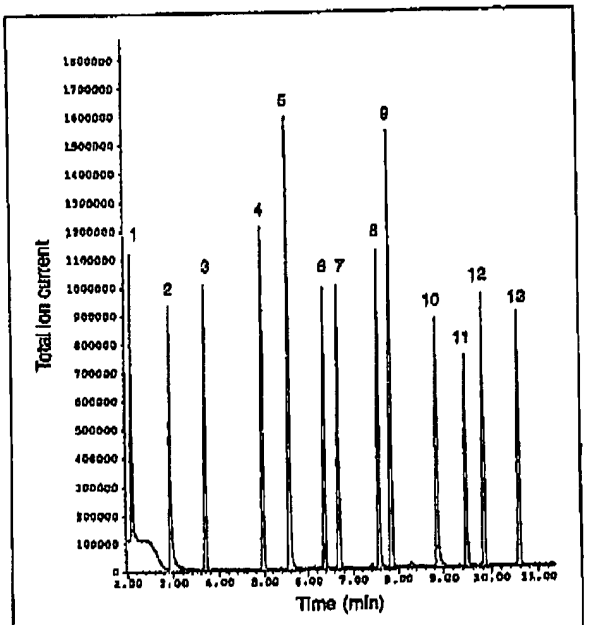

Figure 1. Total ion chromatogram of a headspace extract of several analytes dissolved in dimethylacetamide. Peaks: 1, methanol (140 mg/L); 2, ethanol (145 mg/L); 3, methylene chloride (37 mg/L); 4, chloroform (120 mg/L); 5, acetone (50 mg/L); 6, benzene (26 mg/L); 7, trichloroethylene (43 mg/L); 8, 2-butanone (50 mg/L); 9, n-octane (21 mg/L); 10, 1,4-dioxane (95 mg/L); 11, 2-pentanone (50 mg/L); 12, nonane (21 mg/L); and 13, chlorobenzene (130 mg/L). Dimethylacetamide eluted at 15.5 min.

At an equilibration temperature of 105°C, the analyte signals derived from 1 mL of solution in dimethylacetamide were identical to those produced from 4 mL of solution. The following equation describes the static headspace experiment (7):

$$C_g = C_o (K + V_r)^{-1} \qquad \text{Eq 1}$$

where C_g is the concentration of analyte in the headspace, C_o is the initial concentration of analyte in the solution, V_r is the ratio of the volume of the headspace to the volume of the liquid, and K is the distribution coefficient for material equilibrated between the liquid and vapor phases. Because the vials used have a capacity of 9 mL and the volume of liquid varied between 1 and 4 mL, V_r varied from (9–1)/1 = 8 to 1.25. The distribution coefficients for the analytes in dimethylacetamide at the temperatures used generally exceeded 200 (7), and the volume ratio does not greatly influence the concentration of analyte in the headspace unless small volumes of solution are used. If water was used as a solvent, distribution coefficients for hydrocarbons and other nonpolar materials would decrease dramatically (approaching 1), and the volume ratio could have a substantial impact.

The effect of temperature was examined at 25, 65, 105, and 145°C. Analytes were dissolved in dimethylacetamide at a concentration of 20 to 100 ng/mL. A 0.5-mL aliquot was incubated for 10 min at the test temperature, and the headspace was analyzed by GC–MS using SIM. There was marked degradation in the chromatograms obtained at 145°C, which was ascribed to excess dimethylacetamide being introduced onto the column. Plots of the natural logarithm of peak area versus absolute temperature were linear (correlation coefficient greater than 0.99, chloroform was 0.97) with slopes of about 3%/K (Table II). This implies that the gas-phase concentration approximately doubled for every 20°C rise in temperature.

Estimates of detectability and linearity for select analytes

To ascertain the limit of detection of the method, the signal-to-noise ratio was evaluated in both the scanning and SIM modes. The mass spectrometer was tuned using the self-

directed algorithm supplied by the manufacturer, and no special effort was made to extend sensitivity. Headspace samples were taken after equilibration of 0.5 mL of the test solution for 10 min at 105°C. The concentration of the test solution was adjusted so that it fell within a factor of 2 of what was ultimately estimated to be the limit of detection. Five separate runs were made, and physical measurements were made of the peak height and the width of the baseline. The signal-to-noise ratio (root mean square) was defined as (peak height × 1.4)/(width of the baseline). The average signal-to-noise ratio was used to predict the concentration that would give rise to a signal-to-noise ratio of 3 by linear extrapolation. These numbers are presented in Table II. Analytes could be detected at a concentration of 1 mg/L using the scanning mode. Moreover, a search of the mass spectrum of peaks obtained from the test solution against the Wiley Library using a PBM (reverse) algorithm returned the analyte as the first or second hit. When SIM was used, the detectability increased by a factor of 25 to 100. To examine the linearity of the system, a series of solutions were evaluated between the limit of detection and 1000 mg/L. Successive concentrations were separated by a factor of 3, and one was duplicated within each decade of concentration. The highest concentration that remained on the linear portion of the calibration curve is reported (Table II). Linearity exceeded 4 orders of magnitude.

Table I. Retention Behavior for Selected Compounds on the Capillary Column

	Rtx-200 column			DB-624 column*	
Analyte	Relative retention index	Retention time (min)	Ratio to benzene	Retention time (min)	Ratio to benzene
Methanol	<500	2.51	0.35	2.32	0.25
Pentane	500	2.87	0.40	–	–
Ethanol	537	3.45	0.48	3.13	0.33
Diethylether	579	3.56	0.50	3.29	0.35
Isopropanol	589	4.23	0.59	3.91	0.42
Methylene chloride	594	4.35	0.61	4.38	0.46
Hexane	600	4.44	0.62	5.46	0.58
2-Methyl-2-propanol (t-Butyl)	625	4.98	0.70	4.6	0.49
1-Propanol	645	5.39	0.75	6.02	0.64
Chloroform	660	5.70	0.80	7.92	0.84
Carbon tetrachloride	684	6.19	0.87	–	–
Acetone	687	6.25	0.87	3.67	0.39
Heptane	700	6.53	0.91	10.54	1.12
2-Methyl-1-propanol (Isobutyl)	716	6.86	0.96	9.48	1.01
Benzene	729	7.15	1.00	9.42	1.00
Tetrahydrofuran	736	7.30	1.02	7.74	0.82
Trichloroethylene	745	7.50	1.05	11.64	1.24
1-Butanol	755	7.70	1.08	11.86	1.26
Ethyl acetate	760	7.81	1.09	7.34	0.78
2-Butanone	783	8.33	1.17	7.1	0.75
Octane	800	8.68	1.21	–	–
3-Methyl-1-butanol (Isoamyl)	833	9.33	1.30	17.34	1.84
Toluene	842	9.53	1.33	17.05	1.81
1,4-Dioxane	848	9.65	1.35	13.04	1.38
1-Pentanol	859	9.94	1.39	–	–
Nonane	900	10.70	1.50	–	–
Methyl isobutyl ketone	936	11.38	1.59	16.51	1.75
Chlorobenzene	942	11.48	1.61	–	–
Decane	1000	12.57	1.76	–	–
Undecane	1100	14.29	2.00	–	–
Cyclohexanone	1148	15.07	2.11	–	–
o-Dichlorobenzene	1167	15.37	2.15	–	–
Dodecane	1200	15.91	2.23	–	–
Tetradecane	1400	18.80	2.63	–	–

* This data was reproduced from reference 15 with permission. Column conditions: 30 m × 0.32-mm i.d., 1000-nm film, operating at a linear velocity (helium) of 33 cm/s. Temperature program: hold at 40°C for 5 min then ramp to 90°C at approximately 2°C/min, ramp to 225°C at approximately 30°C/min, and hold for 2 min.

Comparison of water and dimethylacetamide

Signals produced from analytes dissolved in dimethylacetamide were compared with those from substantially aqueous solutions (10% dimethylacetamide in water, v/v). The nonpolar analytes could not be taken through successive dilutions with water in a controlled manner. Solutions (0.5 mL) were equilibrated at 85°C (water) or 105°C (dimethylacetamide) because these were taken to be the highest allowable equilibration temperatures based upon the manufacturer's recommendation (not less than 15°C below the boiling point) and the observation of poor chromatography at 145°C for analytes derived from dimethylacetamide.

An examination of Table II shows that although water generally produces higher sensitivities, the differences are within a factor of 10. For polar analytes with good solubility in water, such as ethanol, acetone, and dioxane, the dimethylacetamide system appeared advantageous. Although the addition of inorganic salts to water has been used to produce a marked reduction in distribution coefficients for polar compounds and to improve sensitivity (7), water eluted during the early part of the chromatogram on this column (Rtx-200) and produced significant peak broadening of methanol, ethanol, and isopropanol.

Determination of acetone in sulfamethazine

The system was applied to the determination of acetone in the sulfonamide antibiotic, sulfamethazine. A 0.2-g portion of the solid sample was dissolved in 0.5 mL dimethylacetamide with 2-pentanone present at a concentration of 2 mg/L to serve as an internal standard. The sample was incubated at 105°C for 15 min and examined by SIM at 43 amu. Four other ions were tracked at the same time to check for addi-

Table II. Figures of Merit for Selected Compounds Dissolved in Dimethylacetamide

Analyte	Concentration[a] (mg/L) Scanning	SIM	Linearity[b] SIM (mg/L)	Temperature coefficient (%/K)	Relative signal strength[c]
Ethanol	2	0.06	610	4.8	3.8
Methylene chloride	0.5	0.006	140	3.3	0.2
Chloroform	1.3	0.01	360	2.3	0.07
Acetone	0.4	5	440	2.9	1
Benzene	0.3	0.002	110	3.2	0.1
Trichloroethylene	0.5	0.006	180	3.7	0.1
Methyl ethyl ketone	0.5	0.008	200	3.2	0.4
n-Octane	0.2	0.006	200	2.9	0.2
Dioxane	1.2	0.02	400	3.6	1.5
Chlorobenzene	1.4	0.01	560	3.9	0.02

[a] Average of 5 determinations and extrapolated to a signal-to-noise ratio of 3.
[b] This is the highest standard evaluated that remained on the linear portion of the calibration curve.
[c] Signal produced by the same concentration in dimethylacetamide incubated at 378 K relative to that from water at 358 K.
[d] A system blank limited the investigation of acetone at low levels.

tional impurities at low levels, and as a result, the repetition rate was limited to 4.8 Hz. Calibration curves were prepared from 0.05 to 6 mg/L by plotting the concentration versus the ratio of the peak area of acetone to that of 2-pentanone (normalized to its concentration and corrected for the blank). The average slope observed for 12 distinct runs spread over 4 months was 0.60 (SD = 0.04) with an intercept of 0.01 (SD = 0.01). In no case did the correlation coefficient fall below 0.997.

Some samples that exhibited acetone concentrations of less than 1 mg/kg were spiked with between 300 and 1000 ng of acetone and demonstrated a recovery of 89% (SD = 4, N=8). This information is presented in Table III. A system blank restricted the limit of detection ($3 \times S_{blank}$, N=51) to 0.3 mg/kg of acetone in the bulk drug.

To determine precision, check samples that contained either 1.4 mg/kg of acetone or 13 mg/kg of acetone in sulfamethazine were evaluated in duplicate with each lot of samples analyzed. This procedure was followed over the four-month interval during which the study was conducted. The same instrumentation and analysts were employed throughout. Same-day precision, at a concentration of 1.4 mg/kg, was 5% (RSD, N = 9 pairs) and same-day precision at a concentration of 13 mg/kg was 3% (RSD, N = 14 pairs). The between-day precision, at a concentration of 1.4 mg/kg, was 13% (RSD), and that at 13 mg/kg was 6% (RSD).

Table III. Recovery of Acetone from Sulfamethazine

Acetone present (mg)	Spiking[a] level (mg)	Acetone recovered (mg)	Percent recovery
41	236	244	86
39	246	252	87
182	709	852	94
202	674	834	94
51	817	815	94
54	782	752	89
98	937	888	84
87	933	903	87

[a] The sample size is 0.2 g, and therefore, a spike of 600 ng is equivalent to a product concentration of 2.5 mg/kg.

Conclusion

Static headspace sampling coupled to narrow-bore capillary GC with MS detection provided an effective means for identifying and quantitating volatile materials in pharmaceuticals. The effective limit of detection in scanning mode was about 1 mg/L for materials dissolved in dimethylacetamide. SIM provided improvements in detectability that approached a factor of 100, and the linearity exceeded 4 orders of magnitude. When water was used as a solvent, more favorable partitioning into the vapor phase was generally observed, but the differences were not overly dramatic, particularly for polar analytes with good solubility in water. This difference can be reduced in a practical sense by the solubility of the drug in the solvent system and by manipulation of the temperature at which the system is equilibrated prior to sampling. Acetone was effectively detected and analyzed at concentrations in the neighborhood of 1 mg/kg in sulfamethazine.

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